Ref:Ro J Neurol. 2017;XVI(Suppl.2)
DOI: 10.37897/RJN.2017.S2.3

BIOINFORMATIC AND COMPUTATIONAL PHARMACOLOGY: NEW PERSPECTIVE IN DEPRESSION TREATMENT IN RISK FACTOR GROUP PATIENTS

A.M. Udrea[1], A. Puia[2], I. Alexandrescu[3], S. Avram[4]

[1]*University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology and Biophysics, Bucharest, Romania*
[2]*University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology and Biophysics, Bucharest, Romania*
[3]*University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology and Biophysics, Bucharest, Romania*
[4]*University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology and Biophysics, Bucharest, Romania*

ABSTRACT

Depression is an illness that affects mostly women, the treatment of this illness is represented by antidepressants and psychotherapy. Even if pregnancy is a wonderful time in a woman's life, the number of women that suffer of depression is growing. Antidepressant medication in pregnancy is not recommended, because of negative effects on new-born. In this paper we use bioinformatic methods to find a new treatment of depression safe to use in pregnancy. Our results show that natural compounds resveratrol (8.67), melatonin (8.58) and linalyl acetate (9.40) have biological activity similar with antidepressants on serotonin transporter. Because majority of antidepressants have serotonin transporter as main target, biological activity on serotonin transporter may indicate that this natural compound could have antidepressant-like activity. Supplementary we made an Absorption, Distribution, Metabolism, Excretion, Toxicity in silico study, to complete the pharmacological profile of these natural compounds, in comparation with antidepressants sertraline and amitriptyline. We conclude that melatonin, resveratrol and linalyl acetate are tolerated well by the human body, and may represent a viable alternative in depression treatment, even for risk factor groups.

Keywords: QSAR, Bioinformatics, Pharmacology, SERT, natural compounds, ADMET.

INTRODUCTION

Depression is an illness that affects women more than men (Albert, 2015). Up to 12% of pregnant women are affected by depression (Grote, 2010). The treatment for depression is generally represented by antidepressant medication and psychotherapy.

Utilization of antidepressant drugs in pregnancy could have negative effects on new-born like malformations. If the medication is taken in the first trimester of gestation; antidepressants could cause a shorter duration of pregnancy, and changes in the foetus development (Yonkers, 2010). The newborns present smaller head circumference, lower Apgar score and lower weight, also the new-borns could present behaviour changes (Marcus, 2009; Wisner, 2009).

This study's aim was to find an alternative depression treatment, using natural compounds. In this study we use resveratrol, a polyphenol found in blueberries (*Vaccinium myrtillus* L.), melatonin an indole produced by pineal gland but also found in goji fruits (*Lycium barbarum L.* and *Lycium chinense* Mill.), and linalyl acetate (*Lavandula angustifolia* Mill.) an ester that is found in lavender essential oil.

In case of melatonin (Tamura, 2008) we find that is safe to use in pregnancy. We find that resveratrol is safe to use during pregnancy in case of rats (Madhyastha, 2013) we don't find data of resveratrol administration on pregnant women. Unfortunately, we are unable to find data regarding the safety of linalyl acetate in pregnancy.

Studies have linked melatonin (Srinivasan, 2009), resveratrol (Ge J-F, 2016) and linalyl acetate (Koulivand, 2013) effect on ameliorating depressive symptoms. The mechanism of action of those molecules is still unknown.

In this study we evaluated if the molecules have biological activity in serotonin transporter (SERT), the main target for clinically drugs used in treatment of depression.

We used predicted values of placental transfer index from Hewitt article (Hewitt, 2007). In our previous work (Udrea, unpublished) we predict the placental transfer index for antidepressants, antipsychotic drugs but also for resveratrol, melatonin and linalyl acetate by developing a QSAR equation (1).

$$TI = 1.68607 - 0.05682 \times a_don + 0.07859 \times logP\ (\text{o/w}) - 0.13854 \times SMR. \quad (1)$$

Results indicate that the most of antidepressants and the natural compound cross the placental barrier, but most antipsychotics do not. Our results are correlated with the negative effects on foetus and new-born, caused by antidepressants (Marcus, 2009; Wisner, 2009).

In addition, we predict the *in silico* Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters for resveratrol, melatonin and linalyl acetate.

We compare the results with the predicted ADMET values of clinically used drugs amitriptyline and sertraline. We have selected those two molecules because they have a similar biological activity with natural compounds on SERT.

ADMET analysis tries to reveal how a drug behaves in the human body. In this study we evaluated the Caco2 permeability, Central nervous system permeability, renal OCT2 substrate, CYP2D6 inhibition, CYP1A2 substrate, Maximum tolerated dose in humans, hERG I and hERG II inhibition.

(i) The Caco2 permeability refer to the ability of a compound to be absorbed.

(ii) The Central Nervous System (CNS) permeability to see if the compounds are distributed in the CNS.

(iii) The renal OCT2 substrate offers information about the possible contraindication regarding co-administrations, and if the compound could be metabolized by kidneys.

(iv) We have used the CYP2D6 and CYP1A2 interaction profile to evaluate the safety of natural compounds regarding liver metabolization.

(v) Regarding the toxicity of the natural compounds we evaluated the maximum tolerated dose on humans and (vi) the *human ether-a-go-go gene* (hERG I and II) inhibition. The hERG I and II inhibition affect potassium ion channels that lead to development of long QT syndrome (Priest, 2008).

METHODS

Molecular data base

To predict the biological activity of resveratrol, melatonin and linalyl acetate on SERT we build a 3D-QSAR model, in this QSAR model we select a learning set of 21 antidepressants and antipsychotic drugs: amitriptyline, citalopram, clomipramine, desipramine, doxepine, escitalopram, fluoxetine, imipramine, lofepramine, paroxetine, sertraline, trazodone, venlafaxine, aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, risperidone, sertindole, zotepine; and a validation set of 7 antipsychotic and antidepressants: bupropion, loxapine, olanzapine, quetiapine, thioridazine, ziprazidone, fluvoxamine; the test series is composed from natural compounds: melatonin, resveratrol and linalyl acetate.

The biological activity K_i (uM) on SERT was collected from PDSP K_i database (PDSP) after we apply the logarithm function (2) to express the K_i as pK_i.

$$log\left(\frac{1}{Ki}(M)\right) \quad (2)$$

Molecular modelling and minimum energy optimization and descriptor calculation

To fulfill our goal we obtained the 3D structure of clinically used antipsychotic drugs, resveratrol, melatonin, linalyl acetate and clinically used antidepressants in format .mol from CHEMBL data base (Team EBIW).

We minimized the molecules using Forcefield MMFF94x at a 0.05 gradient and after we applied Gasteiger partial charges. The minimization of the molecules was done using Molecular Operating Environment 10 (Molecular Operating Environment, 2010.10) software.

We use Pentacle 1.06 software (Pentacle, 1.06), to automatic calculate the GRid-INdependent Descriptors (GRIND).

The power of prediction of our 3D-QSAR model is confirmed by the statistical results (table1).

PLS regression was used in order to identify from a very large set of independent variables the dependent variables. The PLS parameters that we evaluated are: coefficient of correlation (R2), cross-validated coefficient of correlation (Q2), Standard deviation error of calibration (SDEC) and Standard deviation error of prediction (SDEP) presented in Table 1.

TABLE 1. *Statistical parameters for our 3D-QSAR model on SERT.*

statistical parameters	SDEC	SDEP	R2	Q2
QSAR SERT	0.3	0.51	0.96	0.89

In silico ADMET

In silico ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) is an important technique used in drug discovery. The ADMET parameters evaluated how a compound will act inside the human body. It is important to know the ADMET parameters before the administration of a new compound to avoid severe side effects.

In this article we have used pkCSM-pharmacokinetics database (pkCSM), where we introduced the SMILES coding of melatonin, resveratrol, linalyl acetate, amitriptyline and sertraline taken from PubChem database (PubChem).

RESULTS

QSAR results

The 3D-QSAR model equation was applied and led to proper statistical results (R2: 0.96; Q2: 0.89). The power of prediction of our 3D QSAR model is also validated by the best (0.002) and the worst residual values (0.51).

The prediction's accuracy is confirmed by the low residual values; presented in table 2. Results point to similar pK_i activity of the tested natural compounds and commonly used antidepressant drugs.

In the first column we present the molecule name of the learning set compounds. In the second column we present experimental pK_i values of antidepressants and antipsychotic drugs. Third column shows predicted values for antipsychotic, antidepressants melatonin, resveratrol and linalyl acetate. Last column displays residuals values between experimental pK_i values and predicted pK_i values.

TABLE 2. *Predicted and observed and residual pK_i values for antidepressants and antipsychotics drugs and predicted values for natural compounds.*

Molecule name	Observed pK_i	Predicted pK_i	Residuals
Amitriptyline	8.55	8.67	-0.12
Citalopram	9	8.73	0.26
Clomipramine	9.85	9.66	0.18
Despiramine	7.75	8.06	-0.31
Doxepine	7.16	7.57	-0.41
Escitalopram	8.95	8.85	0.09
Fluoxetine	9.09	9.22	-0.13
Imipramine	9.82	9.30	0.51
Lofepramine	7.15	7.18	-0.03
Paroxetine	10.09	9.82	0.26
Sertraline	9.58	9.57	0.007
Trazodone	6.79	6.71	0.07
Venlafaxine	8.12	8.02	0.09
Aripriprazole	5.74	5.86	-0.12
Chlorpromazine	8.88	9.23	-0.35
Clozapine	6	5.48	0.51
Fluphenazine	5.22	5.22	-0.002
Haloperidol	6	5.50	0.49
Risperidone	6	6.04	-0.04
Sertindole	6	6.41	-0.41
Zotepine	6.82	7.35	-0.53
Resveratrol		8.67	
Linalyl Acetate		9.40	
Melatonin		8.58	

Antidepressant range on pK_i is from 6.79 (trazodone) to 10.09 (paroxetine). The Natural compounds values vary from 8.59 (melatonin) to 9.40 (linalyl acetate). The predicted values of melatonin (8.58) and resveratrol (8.67) are similar to pK_i value of amitriptyline, while linalyl acetate value of 9.40 is close to sertraline (9.58).

The similarities in values points to related effects on the serotonin transporter. In figure 1 we present the comparation between experimental pK_i values and predicted pK_i values of antidepressants and antipsychotic drugs from learning set, on 3D-QSAR model on SERT (R2=0.96; Q2=0.89).

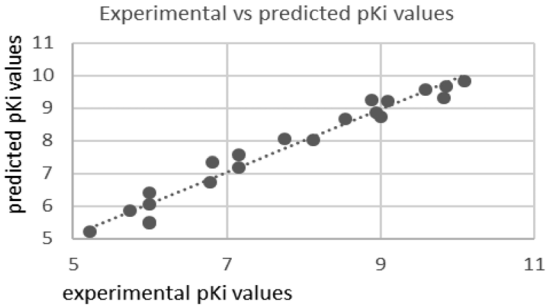

FIGURE 1. *Experimental versus predicted pKi values of drugs from learning set.*

ADMET results

Results of *in silico* ADMET studies show that all te natural compounds present a high Caco2 permeability (all the compounds have a value higher than 0.90 log Papp in 10-6 cm/s, that is considered high).

The natural compounds have a medium, respectively medium-high CNS permeability, in case of resveratrol (-2.09) on the other hand amitriptyline and sertraline are higher -1.41, respectively -1,15. a value higher than -2 is considered that penetrate the nervous system.

Natural compounds and sertraline are not CYP2D6 substrate, but amitriptyline is. Melatonin, resveratrol, amitriptyline and sertraline inhibit CYP1A2 but linalyl acetate shows no inhibition. All compounds except amitriptyline are not renal OCT2 substrate.

The maximum tolerated dose (human) is similar between all the compounds, linalyl acetate has the highest maximum tolerated dose (0.54 log mg/kg/day) and melatonin has the lowest one (0.38 log mg/kg/day).

No natural compound, present hERG I, or II inhibition, unlike sertraline and amitriptyline which both present hERG II inhibition.

The ADMET results for resveratrol, linalyl acetate melatonin and clinically used drugs in treatment of depression sertraline and amytriptyline are presented in Appendix A.

CONCLUSIONS

Based on the high power of prediction of our 3D-QSAR model (R2: 0.96; Q2: 0.89) our study conclusions reveal that melatonin, resveratrol and linalyl acetate, have similar biological activity on SERT with commonly used medication in treatment of depression (amitriptyline and sertraline).

ADMET *in silico* studies indicate that melatonin, linalyl acetate and resveratrol are well tolerated by human body in terms of absorption. Regarding toxicity melatonin resveratrol and linalyl acetate shows no hERG II inhibition, on the other hand amitriptyline and sertraline show inhibitory effect on hERG II.

However, the disadvantage of the natural compounds compared to the clinically used medication is represented by the lower CNS permeability.

Melatonin and resveratrol can be utilized in pregnancy, without the negative effects on foetus or new-borns.

The general conclusion of our study is that melatonin, resveratrol and linalyl acetate can be a reliable substitute to classical antidepressants in case of pregnant women that are suffering from depression.

The natural compounds are well tolerated by the human body, present fewer side effects, and are safe for the foetus and new-born.

REFERENCES

1. **Albert P.** (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience*, 40(4), 219-221.
2. **Ge J. Xu, Y. Qin G. Cheng J. and Chen F.** (2016). Resveratrol Ameliorates the Anxiety- and Depression-Like Behavior of Subclinical Hypothyroidism Rat: Possible Involvement of the HPT Axis, HPA Axis, and Wnt/β-Catenin Pathway. *Frontiers in Endocrinology*, 7:44
3. **Grote, N. Bridge, J. Gavin, A., Melville, J. Iyengar, S. and Katon, W.** (2010). A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. *Archives of General Psychiatry*, 67(10), 1012.
4. **Koulivand, P.H. Khaleghi Ghadiri, M and Gorji, A.** (2013). Lavender and the Nervous System. *Evidence-based Complementary and Alternative Medicine*, eCAM.
5. **Madhyastha S., Sekhar S., Rao G.** (2013). Resveratrol improves postnatal hippocampal neurogenesis and brain derived neurotrophic factor in prenatally stressed rats. *International Journal of Developmental Neuroscience*, 31(7), 580-585.
6. **Marcus S.M**. (2008). Depression during pregnancy: rates, risks and consequences-Motherisk Update. *Can J Clin Pharmacol*. 16(1)
7. **PDSP.** https://pdsp.unc.edu/databases/kidb.php. Accessed January 20, 2017.
8. **Pires D.** pkCSM. http://biosig.unimelb.edu.au/pkcsm. Accessed January 22, 2017
9. **Priest, B. Bell, I.M. and Garcia, M.** (2008). Role of hERG potassium channel assays in drug development, *Channels*, 2:2, 87-93
10. **Srinivasan, V. Smits, M. Spence, W. Lowe, A.D. Kayumov, L. Pandi-Perumal, S.R. Parry, B. Cardinali, D.P.** (2009). Melatonin in mood disorders, *The World Journal of Biological Psychiatry*, 7:3, 138-151
11. **Tamura, H. Nakamura, Y. Terron, M. Flores, L. Manchester, L. Tan, D. Sugino, N. And Reiter, R.** (2008). Melatonin and pregnancy in the human. *Reproductive Toxicology*, 25(3),291-303.
12. **Team EBIW.** ChEMBL. https://www.ebi.ac.uk/chembl/. Accessed January 10, 2017.
13. **The PubChem Project**. National Center for Biotechnology Information. PubChem Compound Database. https://pubchem.ncbi.nlm.nih.gov/. Accessed January 10, 2017.
14. **Udrea A.M., Puia A., *Shaposhnikov* S., Avram S.** Computational Approaches of Therapeutic and Pharmacokinetic Profiles of Natural Compounds at Serotonin Transporter-Innovative Solution in Treatment of Pregnant Woman Patients. *Unpublished.*

15. **Wisner K., Sit D., Hanusa B., Moses-Kolko E., Bogen D., Hunker D., Perel J., Jones-Ivy S., Bodnar L., Singer L.** (2009). Major Depression and Antidepressant Treatment: Impact on Pregnancy and Neonatal Outcomes. *American Journal of Psychiatry*, 166(5), 557-566.

16. **Yonkers K., Lockwood C., Wisner K.** (2010). The Management of Depression During Pregnancy: A Report From the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstetrics & Gynecology*, 115(1), 189.

Appendix A

ADMET predicted values for natural compounds in comparation with amitriptyline and sertraline

Model Name	linalyl acetate	resveratrol	melatonin	sertraline	amitriptyline	Unit
Caco2 permeability	1.63	1.19	1.2	1.44	1.41	log Papp in 10-6 cm/s
CNS permeability	-2.37	-2.09	-2.43	-1.15	-1.41	log PS
CYP2D6 substrate	No	No	No	No	Yes	Yes/No
CYP1A2 inhibitior	No	Yes	Yes	Yes	Yes	Yes/No
Renal OCT2 substrate	No	No	No	No	Yes	Yes/No
Max. tolerated dose (human)	0.54	0.48	0.38	0.45	0.46	log mg/kg/day
hERG I inhibitor	No	No	No	No	No	Yes/No
hERG II inhibitor	No	No	No	Yes	Yes	Yes/No